Clostridium difficile: Review of Treatment & Prevention through Antimicrobial Stewardship

Kim Van Wyk, Pharm.D., BCPS
Mountain-Pacific Quality Health

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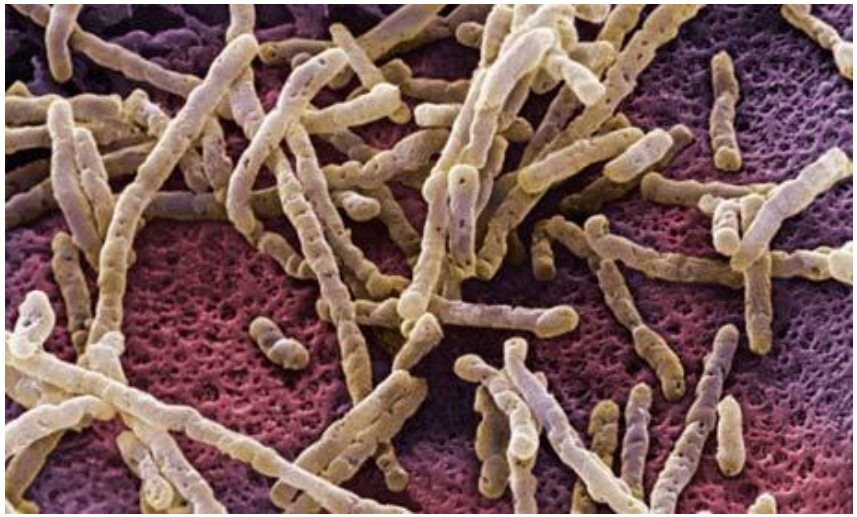
Objectives

- Review epidemiology of *Clostridium diffilcile* infections (CDI) and its impact on morbidity and mortality
- List risk factors for development of *CDI*
- Differentiate the complexities of diagnosing *CDI*
- Describe the management and treatment of CDI
- Understand how the goals of Antimicrobial Stewardship align with the endeavors to decrease healthcare acquired *CDI*
- Differentiate the complexities of diagnosing *CDI*
- Review the strategies of Antimicrobial Stewardship

http://sitfu.com/wp-content/uploads/2011/02/Cdiff.jpg

Clostridium difficile

- 1st described in 1935
- named d/t difficulty to isolate and grow
- spore vs vegetative form
- gram positive rod
- obligate-anaerobe



http://static.guim.co.uk/sys-images/Guardian/Pix/pictures/2013/2/18/1361197460207/Clostridium-difficile-C-d-012.jpg

Clostridium difficile

- various strains
- Opportunistic
- toxin producing in colon
- fecal-oral route spread
- spores can survive outside host for months!
- associated w/ antibiotic use

http://www.nlm.nih.gov/medlineplus/images/clostridiumdifficile.jpg

Antibiotic Associated Diarrhea

- AAD occurs in ~20% of patients receiving antibiotics
- Mechanism
  - Gut flora alterations
    - Disturb carbohydrate and bile acid metabolism resulting in osmotic and secretory-like diarrhea
    - Opportunistic
  - Direct effects on mucous membranes via allergic or toxic effects
  - Changes in gastric motility due to pharmacological effects

History of ABX and CDI

- 1940's introduction of antibiotics
- 1972: clindamycin first approved by FDA
- 1974: *C difficile* era begins with high rates of pseudomembranous colitis (PMC) at hospital SL, MO
- 1978: *C difficile* identified as cause of PMC
- 1989-1992: J strain identified
- 2003-2006: NAP1/BI/027 hypervirulent strain identified
- 2004: rifaximin (Xifaxan) approved by FDA
- 2011: fidaxomicin (Dificid) approved by FDA

CID 2008;46:S4-11

Prevalence & Incidence

- From 2000-2009 (most recent data from MMWR)
  - Hospital discharge diagnosis doubled
  - Primary CDI diagnosis more than tripled
- Accounts for 20-30% of AAD cases
- Most common cause of infectious diarrhea in healthcare setting
- >90% of *C. difficile* deaths occurred in pts >65 years

MMWR 2012;61:157-162
Infect Control Hosp Epidemiol 2010;31: 431-455
http://www.cdc.gov/Features/VitalSigns/HAI/

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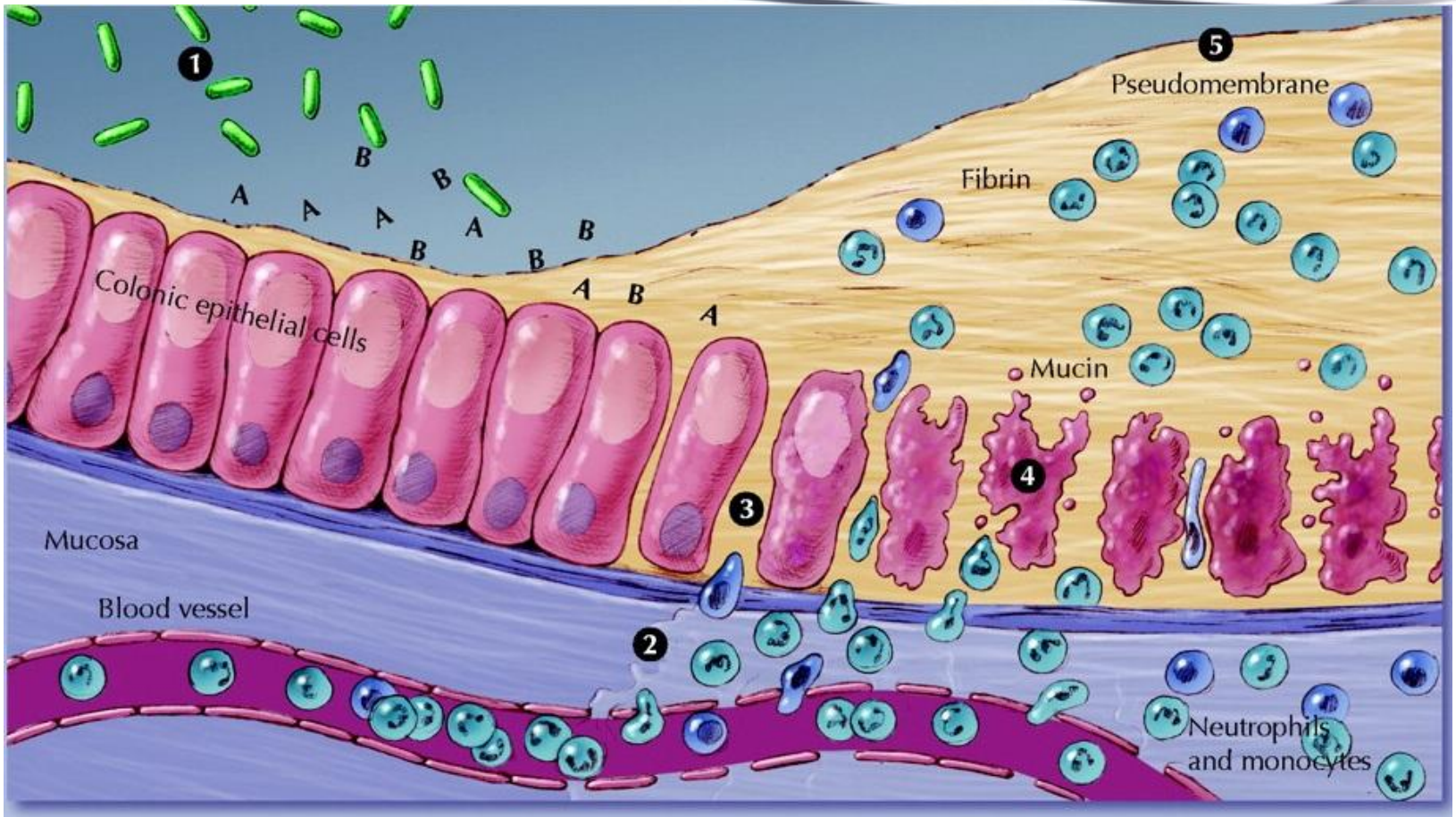
Strains of CDI

- Not all strains lead to disease
  - Non-pathogenic strains do not produce toxins
- Toxin producing strains
  - Toxin A: enterotoxin
  - Toxin B: cytotoxin: more virulent
  - Binary Toxin: 3rd toxin in hypervirulent strain
- "J" Strain
  - Clindamycin resistant
  - Epidemics in late 1980s and 1990s



C. difficile vegetative cells produce toxins A and B and hydrolytic enzymes (**1**). Local production of toxins A and B leads to production of tumour necrosis factor-alpha and proinflammatory interleukins, increased vascular permeability, neutrophil and monocyte recruitment (**2**), opening of epithelial cell junctions (**3**) and epithelial cell apoptosis (**4**). Local production of hydrolytic enzymes leads to connective tissue degradation, leading to colitis, pseudomembrane formation (**5**) and watery diarrhea.

http://www.cdiff-support.co.uk/images/cDiffLarge.jpeg

BI/NAP1/027 strain

- Produces the binary toxin: role not fully understood
- Increased production of toxin A & B
- Resistance to fluoroqinolones
- Higher rates of infection & relapse
- Poorer response to therapy
  - Specifically fidaxamicin (more to come about this)

N Engl J Med 2005;353: 2433-41.
Lancet 2005;366(9491): 1079-84.

Risk factors for CDI

- Antibiotic use
  - Disrupts normal flora
  - Role in hypervirulent strains due to developed resistance
  - Most common antibiotics associated
    - clindamycin
    - fluoroquinolones
    - Broad spectrum cephalosporins
    - Broad spectrum penicillins

Infect Control Hosp Epidemiol 2010;31: 431-455

Risk factors for CDI

- Advanced Age
  - Co-morbidities
  - Healthcare exposed
  - Diminished immune response
- Cancer chemotherapy
  - Antimicrobial like actions
  - Immunosuppressive actions
- HIV infection
  - Immuno-supression & prophylaxis therapy
- Gastrointestinal surgery
- Tube feedings

Infect Control Hosp Epidemiol 2010;31: 431-455

Risk factors for CDI

- Acid Suppressive agents
  - 2010 IDSA/SHEA guidelines
  - Controversial & evidence is confounding by other factors
  - 2012 meta analysis
    - Concluded a probable association
    - Association of PPI use with CDI
      - OR 1.74 (95% CI 0.47-2.85, p<0.001) PPI users vs non-users
    - Association of PPI use and recurrent CDI
      - OR 2.51 (95% CI 1.16-5.44, p=0.005)
- **Is this on the radar at your facility?**

Infect Control Hosp Epidemiol 2010;31: 431-455
Am J Gastroenterol 2012;107:1011-9.

Testing Methods for CDI

Stool Culture

- High sensitivity (~95%)
  - Negative result is reliable
- High Specificity
  - However—No distinction between toxin producing strains
  - Positive result requires confirmation of toxin
- Labor intensive (3-6 days)
- Role in epidemiologic studies

Toxigenic Culture

- High sensitivity (~85%)
- High specificity (~99%)
- Very slow turnaround to be clinically useful
- Considered gold standard
- Also referred to as cytotoxin assay

http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/infectious-disease/clostridium-difficile-infection/

Testing Methods for CDI

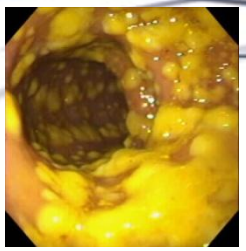
ELISA for Toxins

- lower sensitivity (~75%)
  - Negative test not as reliable
  - d/t amount of toxin needed to test positive
- High specificity (~99%)
  - Positive test is reliable
- Can detect toxin A, toxin B or both
- Easy to perform

EIA for GDH

- Very low sensitivity
- Low specificity
  - No distinction between toxin producing strains
- Requires confirmatory test
- Role as screening test
- FAST and Cheap
- Better options available

http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/infectious-disease/clostridium-difficile-infection/



Testing Methods for CDI

http://drugline.org/img/ail/2845_2864_1.jpg

PCR

- High sensitivity (~95%)
- High specificity (~100%)
- Detects toxin A & B genes
- Easy to perform stand alone test
- $$$
- Potential for false positive results

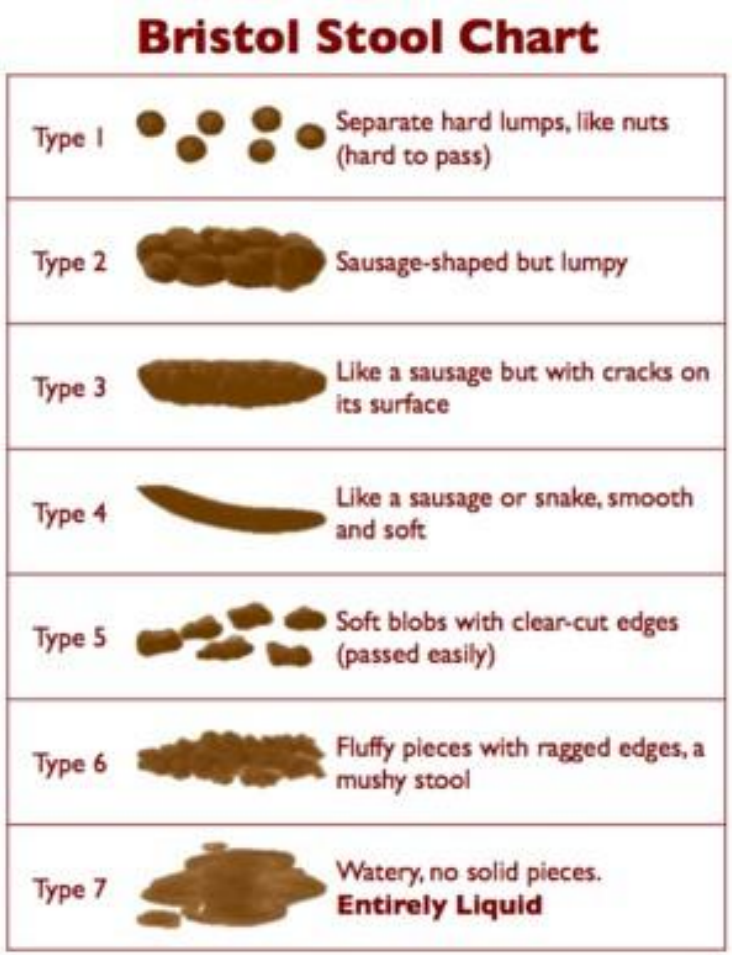
Endoscopy

- Helpful as adjunctive tool for uncertain diagnosis
- Low sensitivity (~50%)
  - not all pts experience PMC
- High specificity (~100%)
- Disadvantages
  - Cost
  - Invasive
  - Risks of perforation

http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/infectious-disease/clostridium-difficile-infection/

Testing Pearls

- Only perform laboratory testing on unformed stool only!
  - Exception: suspected ileus
- > 3 unformed stools in 24 hour period
- Consider recent laxative use



http://thewvsr.com/bristolstoolchart.htm

Prevention & Management: Infection control

- Contact precautions
  - Isolation: Private pt rooms or cohort infected pts
  - Dedicated patient care items
  - Gown & gloves…easy access
  - Policy in place for d/c contact precautions
    - Controversial of who and when…
- Hand hygiene
  - Alcohol based gels vs soap and water
  - Is it ever appropriate to just use alcohol based gels?

Infect Control Hosp Epidemiol. 2008;29:S81-S92.

Prevention & Management: Infection control

- Environmental Cleaning
  - Clean then Disinfect
    - 1:10 dilution sodium hypochlorite (bleach)
    - Allow bleach contact time of at least 10 min
  - Monitor cleaning and disinfecting protocols
    - DAZO
    - ATP
  - Terminal Cleaning
    - Definition
    - When does it occur?
      - Removal of contact precautions
      - At patient transitions
      - pts who have cleared the infection & precautions are d/c'd?

Treatment

- Based on episode and severity
  - Initial episode
    - Mild/moderate
    - Severe
    - Severe complicated
  - 1st recurrence
  - 2nd recurrence
  - Subsequent relapse

Treatment Pearls

- Discontinue causative antibiotic when possible
  - if need to continue, consider changing to a different agent less likely to promote CDI
- Manage fluid and electrolyte balance
- Antiperstaltic agents

REVIEW ARTICLE

Antimotility Agents for the Treatment of *Clostridium difficile* Diarrhea and Colitis

Hoonmo L. Koo,[1,2] Diana C. Koo,[2] Daniel M. Musher,[1,4] and Herbert L. DuPont[1,2,3,5]

[1]Department of Medicine, Division of Infectious Diseases, Baylor College of Medicine, [2]University of Texas–Houston School of Public Health, [3]University of Texas Medical School, [4]Michael E. DeBakey Veterans Affairs Medical Center, and [5]St. Luke's Episcopal Hospital, Houston, Texas

(See the editorial commentary by Gerding on pages 606–8)

Clin Infect Dis 2009; 48: 598-605.

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Initial episode treatment

Metronidazole: mild/moderate

- Dose dependent peripheral neuropathy
- Nausea
- Metallic taste
- Alcohol consumption
  - Disulfiram-like reaction
- Dose
  - 500mg po tid x 10-14d
  - 250mg po qid x 10-14d
  - 500mg IV q8h
- Not FDA approved

Vancomycin: severe

- Must be oral
- Not systemically absorbed
- Vancocin® $$$
- Oral solution from IV form
  - Palatability issue
- Dose
  - 125mg-500mg po qid
  - Evidence show no sig. diff in response or failure rates
  - Guidelines embrace 125mg
- FDA approved

Am J Gastroenterol 1997; 92(5): 739-750

Treatment

First recurrence

- Confirm diagnosis
- Repeat initial suggested regimens
  - Preferential vancomycin
- Alternative option
  - Risk factor assessment
    - fidaxomicin 200mg po bid x10d

Up to 25% of patients experience recurrent CDI within the first 30 days after initial antibiotic treatment

N EnglJ Med 2011;364: 422-431

Second recurrence

- Confirm diagnosis
- Vancomycin taper example
  - 125mg po qid x7-14d
  - 125mg po bid x7d
  - 125 po qday x7d
  - 125mg po every other day x7d
  - 125mg po every 3rd d x 14d
- Alternative option
  - Risk factor assessment
    - fidaxomicin 200mg po bid x10d

Clin Microbiol Infect 2012;18:28-35.

Other treatment options

fidaxomicin (Dificid®) $$$

- FDA approved : treatment
- Minimal systemic absorption
- Stays in the gi tract
  - 92% excreted in feces
- Macrocylic antibiotic class
- Inhibits sporulation
- Bactericidal
- Minimal effect on normal colonic flora
- Long post-antibiotic effect

rifaximin (Xifaxan®)

- Off label use
- Small body of literature
  - May decrease incidence of self reported diarrhea
- Used in combo w/ vanco
  - Used as a chaser
- Resistant concern if previous rifamycin exposure
- Role is unclear
- If tried: Do NOT use alone!

Defining severe disease

- Guidelines
  - WBC >15,000 cells/microL or SrCr ≥ 1.5 baseline
- Point system
  - 1 point: age>60 years, temp >39.3C, serum albumin < 2.5mg/dL, WBC > 15,000 cells/microL
  - 2 points: ICU status or endoscopic evidence PMC
  - ≥ 2 points was considered severe
- Phase 3 trial
  - ≥ 10 BMs/day, WBC ≥ 20,000 cells/microL or severe abdominal pain

Clin Infect Dis. 2007;45(3):302

Other Treatment Strategies anion-binding resins

- Role in binding toxins (as well as oral vanco)
- Current 2010 guidelines do not embrace
- No evidence to support as primary therapy
- Evidence for adjunctive therapy is limited
  - 11 pts treated with tapered vanco and cholestipol
  - Asymptomatic at f/u of 6 weeks
- If utilized for recurrent CDI dosing considerations with cholestyramine

Am J Gastroenterol. 1982;77(4):220.
Infect Control Hosp Epidemiol 2010;31: 431-455

Other Treatment Strategies Probiotics

- 2010 guidelines do NOT recommend for prevention or treatment
- Small body of evidence for use in recurrent CDI
- Proceed with caution
  - Probiotics are not regulated
  - Cases of causing fungemia and bacteremia reported
- Need for further investigation

Beneficial Microbes, March 2013; 4(1): 39-51

Wageningen Academic Publishers

Probiotics in *Clostridium difficile* infection: reviewing the need for a multistrain probiotic

M. Hell[1,2], C. Bernhofer[1], P. Stalzer[1,2], J.M. Kern[2] and E. Claassen[3,4]

Am J Gastroenterol 2006;101:812-22.
. *JAMA* 1994;271:1913-8

Other Treatment Strategies
Fecal Transplant

- Emerging treatment option for recurrent CDI
  - Positive results
- Recent meta-analysis published March 2013
  - Concluded that strategy holds much promise
  - RCTs are still needed
  - "Safe" approach to the procedure from donor collection to actual transplant

Am J Gastroenterol. 2013 Mar 19. doi: 10.1038/ajg.2013.59. [Epub ahead of print]

Other Treatment Strategies

IVIG

- Evidence is not conclusive
- Reports of success
- Largest study found no benefit ---limitations
- Very costly intervention
- Many adverse effects

Monoclonal antibodies

- Randomized, double-blind, placebo controlled study
  - Pts infused with MAB against toxins A& B
  - Rate of CDI recurrence
    - 7% vs 25%, $p<0.001$
- actoxumab & bezlotoxumab
  - Phase 3 studies for treatment of CDI

N Engl J Med 2010;362:197-205.

Other Prevention Strategies Antimicrobial Stewardship

- Embraced by 2010 guidelines to implement stewardship program
- Best when utilized with other strategies
- Multidisciplinary

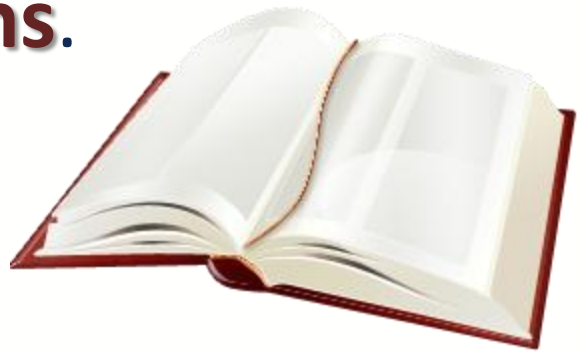
Antimicrobial Stewardship

…**coordinated interventions** designed to improve and measure the **appropriate use of antimicrobial agents** by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy, and route of administration.

Infect Control Hosp Epidemiol 2012; 33(4): 322-327

Antimicrobial Stewardship

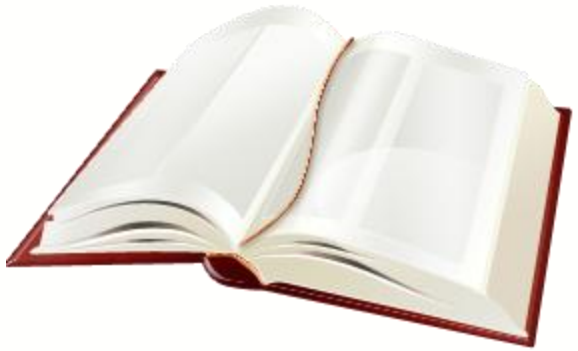
…achieve **best clinical outcome** related to antimicrobial use while minimizing toxicity and other adverse events, thereby **limiting** the selective pressure on bacterial populations that drives the emergence of **antimicrobial-resistant strains**.



Infect Control Hosp Epidemiol 2012; 33(4): 322-327

Defined by AHRQ

…a **systematic approach** to developing coordinated interventions to **reduce overuse** and **inappropriate selection of antibiotics**, and to achieve optimal outcomes for patients in cost-effective ways.



Ultimate Goals

- Optimize clinical outcomes
  - Improve clinical cure rates
  - Reduce length of stay
  - Reduce health care money spent
  - Reduce morbidity and mortality
- Minimize unintended consequences of antimicrobial use
  - Emergent resistance
  - Selection of pathogenic organisms (e.g., *Clostridium difficile*)
  - Toxicity

Clin Infect Dis 2007;44:159-77

Core Strategy: "Foundational"

Prospective audit with intervention & feedback

- Barriers
  - Labor and clinical skill intensive
  - Difficulty in identifying patients with inappropriate therapy
- Possible solutions
  - Utilized computerized systems to screen patients
  - Choose one target – *start small*
    - Selected antimicrobial agents (broad spectrum, $$$, toxic agents)
    - Resulted cultures (both positive and negative cultures)
    - Specific disease state (CAP, Sepsis, UTIs)

Clin Infect Dis 2007;44:159-77

Core Strategy: "Foundational"

Formulary restriction & preauthorization

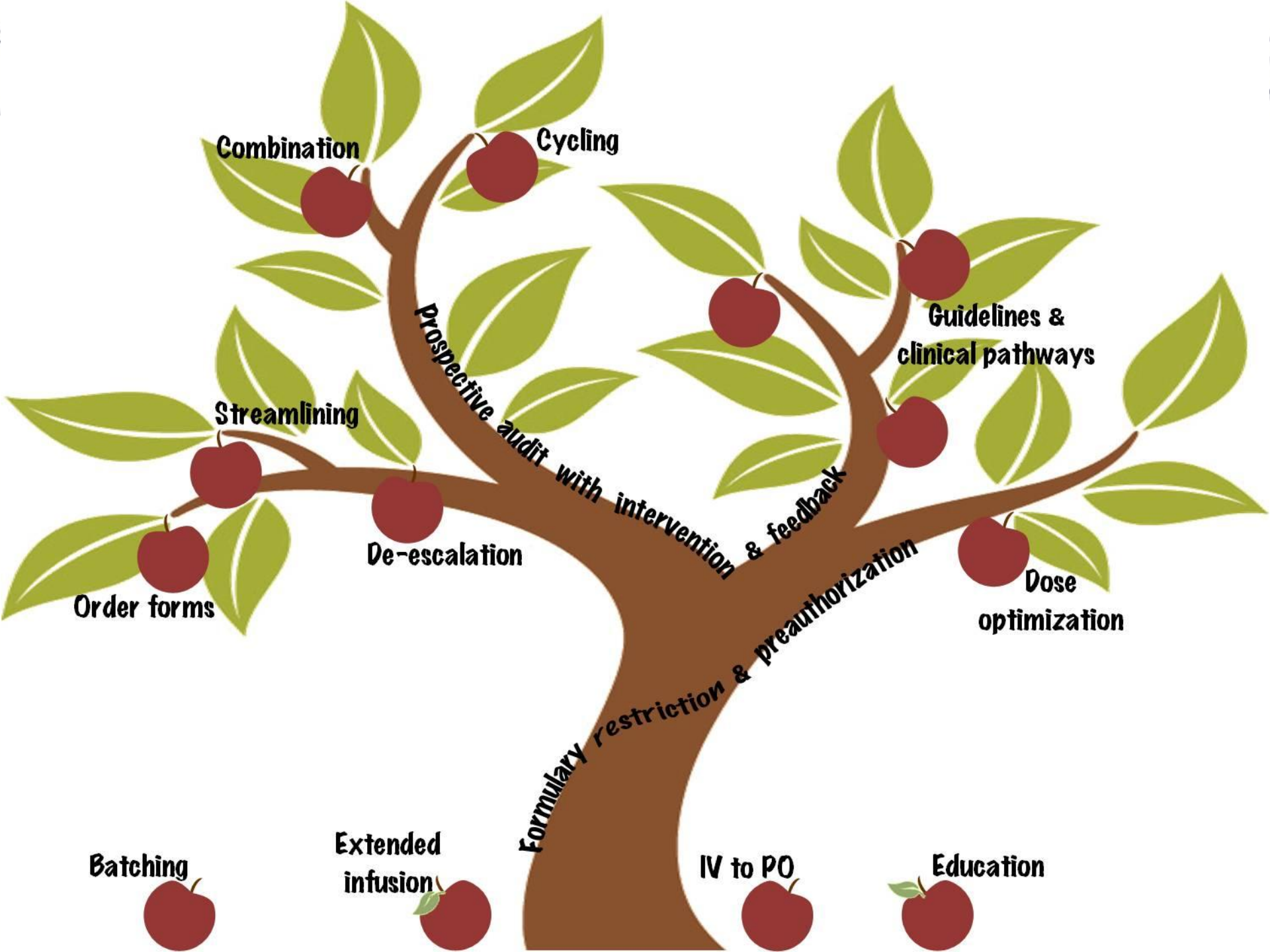
- Barriers
  - Potential to delay therapy initiation
  - Perceived loss of prescriber autonomy
- Possible solutions
  - CPOE (computerized physician order entry)
  - Policies and procedures for immediate dispensing of first dose
  - Require ID or Rx consult for certain antimicrobials

Clin Infect Dis 2007;44:159-77

Supplemental Strategies

- Antimicrobial cycling
- Combination therapy
- Education
- Guidelines and clinical pathways
- Antimicrobial order forms
- Streamlining or de-escalation of therapy
- Dose optimization
- Parenteral to oral conversion

Clin Infect Dis 2007;44:159-77


Combination
Cycling
Prospective audit with intervention & feedback
Guidelines & clinical pathways
Streamlining
De-escalation
Order forms
Dose optimization
Formulary restriction & preauthorization
Batching
Extended infusion
IV to PO
Education

Strategies to Gain Momentum

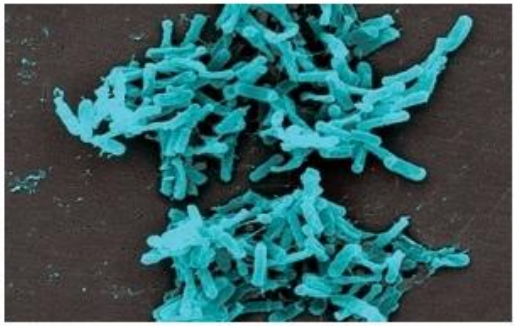
Low-Hanging Fruit

- Most obtainable strategies with limited resources
- Mostly pharmacy-driven approaches
  - IV to PO ($)*
  - Extended infusion ($)*
  - Therapeutic/formulary substitution
  - Formulary restriction
  - Batching of IV antimicrobials ($)

Clin Infect Dis 2012;55:587-92
J Antimicrob Chemother 2009;64: 188-99
Am J Health-Syst Pharm 2011;68: 1521-6

Healthcare Business News

Expanded efforts against C. diff haven't reduced infections: survey



By Bucher Landen
Posted: March 11, 2013 - 12:01 am ET
Tags: Costs, Infection Control, Patient Safety, Staffing

Efforts to curb the spread of Clostridium difficile are increasing, yet are not having much of an effect on the infection rate for the intestinal superbug, **according to a national survey of infection preventionists (PDF)**.

Sponsored by the Association for Professionals in Infection Control and Epidemiology, the survey showed that while 70% of infection preventionists have adopted additional practices to halt the spread of C. diff since March 2010, only 42% have experienced a decline in the infection rate. In fact, 43% have not noticed any improvement.

"We are encouraged that many institutions have adopted stronger measures to prevent" C. diff infections, Jennie Mayfield, APIC president-elect and clinical epidemiologist at Barnes-Jewish Hospital, St. Louis, said **in a release**. "But as our survey indicates, more needs to be done to reduce the spread of this infection."

Mayfield expressed concern that staffing levels aren't sufficient to deal with C. diff. Only 21% of survey respondents said they had added infection prevention staff during the three-year period.

And although 92% of the 1,087 respondents said they had

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- Largest nurse staffing organizations

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Conclusions

- CDI remains a challenging HAI as evidenced by the increasing morbidity and mortality
- Metronidazole remains the first line treatment for mild to moderate CDI, whereas oral vancomycin is the preferred regimen for severe CDI
- Treatment strategies for recurrent CDI are “branching out” from the traditional antibiotic treatment approach
- Prevention strategies that involve an interdisciplinary approach are guideline embraced

Questions?

Kimberly Van Wyk, PharmD, BCPS
ADE Project Lead
Mountain-Pacific Quality Health
Phone: 406-457-5827
kvanwyk@mtqio.sdps.org

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